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Original article

Benefits of pamidronate in children with osteogenesis imperfecta: an open prospective study

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Abstract

Objectives.– To study the efficacy of pamidronate in children with osteogenesis imperfecta (OI).

Patients and methods.– Twenty-nine patients (median age 8.7 years), were given pamidronate in cyclic infusions of 3 days. Patients received 3–13 cycles (median 6), at a dose of 0.5 mg/kg/day in infants (below 2 years of age) and 1 mg/kg/day in children (2 years and older). The interval time between cycles was 2 months in infants and 4 months in children. The median follow-up was 16 months. All patients received daily supplementation of calcium, vitamin D and physical rehabilitation. Assessments were performed at baseline and before each cycle. Fracture rate under treatment was compared to the one in the pre-treatment period.

Results.– Pain decreased after the first infusion cycle ($P < 0.0001$). The median of fracture incidence decreased from 15 to 0.5 per year in infants and from 2.0 to 1 per year in children ($P = 0.04$). Alkaline phosphatase decreased by 31.2% and *N*-telopeptide collagen cross-links decreased by 61.8% ($P < 0.001$). Bone mineral density (BMD) of the spine increased by a median of 55.4% ($P < 0.001$). *Z*-scores increased from a median of –4.7 to –2.6 ($P < 0.001$). The femoral neck, BMD increased by a median of 16%. The area of the first four lumbar vertebrae increased by a median of 21.5% ($P < 0.001$). No adverse effect on growth or on fracture healing was observed. Side effects were symptomatic hypocalcemia in one infant, and the transient acute phase reaction.

Conclusion.– Pamidronate increases BMD, decreases bone remodeling markers, pain and fracture rate in infants and children with OI.

Keywords: Children; Fracture; Osteogenesis imperfecta; Pamidronate

1. Introduction

Osteogenesis imperfecta (OI) is a heterogeneous group of disorders characterized by bone fragility and skeletal deformities, affecting approximately 1/20 000 births. It is estimated that 90% of cases of OI are positive for collagen type 1 mutations. A collagen type 1 molecule consists of three polypeptide chains (two α 1 and one α 2 chain) that form a triple-helical structure. For the three chains to intertwine correctly, they must have a glycine residue at every third position. The most typical sequence abnormality associated with OI is a point mutation that affects a glycine residue in either COL1A1 or COL1A2. Cells harbouring such a mutation produce a mixture of normal and abnormal collagen. The resulting phenotype can vary from very mild to lethal depending on which of the two α chains is affected, the position in the triple helix at which the substitution arises, and which aminoacid is substituted for glycine [1]. More than 200 mutations have been identified. The transmission mode of the disease is autosomal dominant, but autosomal recessive transmission and sporadic mutations, have been described.

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In addition to being the principal element in bone matrix, collagen type I α is present in ligaments, skin, sclerae, and dentin. Clinical manifestations are extremely heterogeneous, ranging from stillbirth to deafness or fracture later in life. Based on the clinical findings and mode of inheritance, several types of OI have been described by Sillence et al. [2]. Type I is the milder form, Type II is an extremely severe type usually lethal in utero or a few days or weeks after birth. Type III is the classic variant of OI characterized by the presence of major skeletal deformities and type IV is a form of moderate severity. Glorieux et al. [3,4] have shown that type IV can be subdivided into three different groups—IV, V, and VI—according to the radiological and histomorphometric features. Recently, another novel phenotype of the disease called type VII was described [5]. The main problem in OI is related to bone formation, but, it has been shown that increased bone remodeling may play a contributing role in this disorder [6]. These findings led some authors to conduct studies [7–14], which showed that a bisphosphonate, pamidronate, a potent inhibitor of bone resorption, in cyclic infusions, is of benefit to children with OI.

The purpose of this prospective study was to confirm the efficacy of pamidronate infusion in reducing pain and fracture incidence, improving functional status and bone mineral density (BMD) and decreasing the biochemical parameters of bone remodeling, in infants and children with OI treated for at least 1 year.

2. Methods

2.1. Patients

Between January 1999 and November 2001, 71 patients were diagnosed as having OI in our department. Indications for pamidronate treatment included: severe form of OI (type III and IV), children with type I who suffered of chronic bone pain or vertebral fractures. Thus, 43 children were treated. Only the data of 29 children (17 boys and 12 girls) who received at least 1 year of treatment were used for the aims of this study. The group included nine familial and 20 sporadic cases. At the first visit, seven children were under 2 years of age and 22 were 2–16 year-old. Seven children were diagnosed as having type I OI, 17 had type III and five had type IV. Twenty-two children had long bone fractures during their first year of life including 13 with fractures at birth.

Patients were followed-up to 34 months (median 16 months).

2.2. Treatments

Pamidronate (Aredia*, Novartis) was administered intravenously in cycles of three consecutive days at a dose of 0.5 mg/kg/day given every 2 months in infants, and 0.5 mg/kg the first day of the first infusion cycle, followed by 1 mg/kg/day thereafter given at 4-month intervals in children older than 2 years [9,10]. Over all, the cumulative dose was 9 mg/kg/year and 8.5 mg/kg/year in infants and children, respectively. The number of infusion cycles per child was 3–13 (median 6).

At the beginning of pamidronate infusions, all patients received a daily supplementation of 1200 IU of vitamin D and 250 mg of calcium when body weight was < 15 kg, 500 mg of calcium if body weight was ≥15 kg. The dose of vitamin D was then periodically adjusted in order to avoid hypercalciuria and nephrocalcinosis. Paracetamol at a dose of 15 mg/kg/day was given to children who developed fever.

Besides medical treatment, all children received physical rehabilitation including motor guidance, global strengthening of muscles, and proprioception. Seventeen children underwent surgery, which included oseotomy and/or medullary rodding for correction of long bone deformities.

2.3. Assessments

Clinical evaluation including height, weight, pain, fracture rate, and patient's caregiver assistance was performed at baseline and the day of admission for each cycle. Height and weight measurements were converted to age and sex specific *Z*-scores using French references [15]. Length at birth was obtained from the parents or looked up in the medical record.

Pain was assessed by asking the children and/or their parents about the estimated number of days with pain or signs of pain per week.

Patient's caregiver assistance was evaluated in children older than 2 years using the Paediatric Evaluation of Disability Inventory (PEDI [16]), which provides scores for 20 complex functional activities: eight in the self care domain, seven in the mobility domain and five in social functional domain. Each activity is assessed using a six point scale as follows: five: independent, four: supervision, three: minimal assistance, two: moderate assistance, one: maximal assistance, zero: total assistance.

Fracture data were collected by reviewing the hospital chart of each patient for fractures occurring before treatment and by history and clinical assessment for those occurring during treatment. The incidence of fractures was assessed by calculating the annualised fracture rate. At baseline, this fracture rate was the number of fractured long bone segments before starting treatment divided by the duration in years between the first fracture and infusion. In those treated before the age of 1 year, this duration was annualised by dividing the number of months by 12. After an overnight fast, serum calcium, phosphate, alkaline phosphatase, creatinine (using calorimetric technique, ROCHE), serum 25 hydroxy (OH) vitamin D, and parathormone (PTH) levels were measured at baseline and before each infusion cycle. 25OH vitamin D was measured by chromatography (normal range: 13–40 ng/ml), PTH was measured by radio immuno assay (normal range: 10–65 pg/ml). Measurements were repeated during the infusion cycle if the patient developed clinical symptoms. The urinary excretion of calcium and of *N*-telopeptide collagen cross-

links (NTX) were measured on a urine sample and calcium/creatinine ratio and NTX/creatininuria (NTX/Cr) ratio were determined at each cycle. Renal ultrasound and plain X-ray of the kidneys, ureters, and bladder (KUB) were performed if hypercalciuria was detected (urinary calcium/creatinine ratio > 1 mmol/mmol before the age of 4 years and > 0.5 mmol/mmol in older children). NTX was measured by enzyme linked immunosorbent assay (ELISA, Nordic Bioscience Diagnostics). Normal range for NTX/Cr is very wide in children and varies from 3289±299 to 149±50 nmol/mmol according to the age group.

Bone mineral density (BMD g/cm^2) and the area of the first four lumbar vertebrae were measured by dual energy X-ray absorptiometry (QDR 4500, Hologic, Bedford MA, USA) at baseline, and then at 4–8 month-intervals. Low-density software was used for infants and for some older children with very low BMD. The difference between the actual spine BMD and the normal one was calculated and expressed in standard deviation, according to French reference values [17]. The *Z*-score was calculated as the ratio of (BMD patient – BMD controls)/SD controls of same age in children treated after the age of 1 year, as our references do not provide normal values for the younger group. BMD of the left femoral neck was measured only in nine children because of technical difficulties related to abnormalities of femoral neck.

Anteroposterior and lateral radiographs of the thoracic and lumbar spine at baseline and after follow-up of at least 1 year were available in 24 patients. All the vertebrae from T4 to L5 were subjected to a visual qualitative evaluation looking for vertebral deformities by two investigators (C.R and V.F), with consensus reading if inter-reader disagreement.

2.4. Statistical analyses

Values are expressed as median (minimum–maximum). Paired *t*-test was used to compare clinical, biological, and densitometric parameters before and after treatment. Due to the small number of subjects in each subgroup (seven infants and 22 children), analyses were done for the whole group and not for each subgroup separately, except for the PEDI. Analyses were performed using SPSS software version 10.0 (SPSS, Chicago, Illinois).

3. Results

The clinical characteristics of the patients at baseline and end of the study are shown in Table 1.

The number of painful days per week decreased in all patients after the first infusion cycle ($P < 0.0001$). Ten children experienced a recurrence of pain in the days preceding the second or the third cycle, but this rebound phenomenon was not observed after the third cycle.

In children older than 2 years, PEDI scores for self-care and mobility domains increased with treatment (P =0.004 and $P = 0.001$, respectively) (Table 1). At baseline the mobility scores were obviously lower in children with type III than in others (18 vs. 32). Children with type I, had very good scores at baseline, which did not change with treatment, but the painless status allowed them to increase the level of their physical activity. Four children were able for the first time, to do sport at school at the end of the study.

At birth and at the beginning of treatment, the children were short for age. Although they gained height and weight significantly during treatment ($P < 0.001$), their height and weight *Z*-scores did not change (Table 1).

The median of annualised fracture rate decreased during treatment both in infants and children ($P = 0.04$). Ten children (34%) had no peripheral fractures during treatment. No delay in healing of fractures was observed, and in children who underwent surgical corrections of long bone deformities, post-operative courses were uneventful.

The densitometric characteristics of the study population are shown in Table 2. The baseline values and changes in BMD over time for 24 patients aged more than 1 year at baseline are shown in Fig. 1. The BMD increased by a median of 55.4% ($P < 0.001$) and *Z*-score improved from a median of –4.7 to –2.6 ($P < 0.001$). The area of the first four lumbar vertebrae increased by 21.5% ($P < 0.001$). New deformities, on previously normal vertebrae were observed in two patients including one traumatic vertebral fracture. At the femoral neck, BMD measured in nine children increased by 16%.

The baseline values of total alkaline phosphatase and NTX/Cr ratio were above the upper limit of normal range in 18 and 16 patients, respectively. The highest values of NTX/Cr were observed in type III patients (data not shown). At the end of the study, these values decreased by a median of 31.2% and 61.8%, respectively ($P < 0.001$).

Table 1
Clinical characteristics of the study population at baseline and at the end of the study

	Height (cm)	Height *Z*-score	Height at birth *Z*-score	Weight (kg)	Weight *Z*-score	Pain (days/week)	* PEDI self care	PEDI mobility	PEDI social function	Annualized fracture rate
Children n = 22 age (years): 2.6–16.1										
Baseline	126.5 (77–160)	–1.3 (–8.7; 0.6)	–2 (–6; 0)	27 (9–56)	–0.5 (–6; 3.3)	7 (0–7)	35 (6–40)	24 (2–35)	25 (15–25)	2.0 (1–7.7)
Final	132 (83–169)	–1.3 (–8.2; 0.4)		30 (10–60)	–0.5 (–6; 3)	0 (0–1)	40 (24–40)	33.5 (6–35)	25 (15–25)	1 (0–7)
Infants n = 7 age (months): 1–24										
Baseline	58 (40–82)	–4.5 (–7; –1.5)	–3.5 (–7; –2.5)	4.7 (2.5–10)	–3 (–4; –1.5)	7 (0–7)	** NA	NA	NA	15 (2.4–90)
Final	71 (55–85)	–5.2 (–7; –2)		8.3 (5.5–12)	–3.3 (–4; –3)	0 (0–3)	NA	NA	NA	0.5 (0–1.7)

Values are median (min–max). * PEDI, Paediatric Evaluation of Disability Inventory. ** NA, not applicable.

Table 2
Radiological, densitometric, and biochemical characteristics of the study population at baseline and at the end of the study

	L1–L4 area (cm^2)	BMD * L1–L4 (g/cm^2)	BMD spine *Z*-score	Calciuria mmol/mmol cr	NTX/Cr ** mmol/mmol cr	Alkaline phosphatase (IU/l)
Age >2 years (n = 22)						
Baseline	29 (15–47)	0.34 (0.11–0.69)	–4.4 (–8; –0.4)	0.4 (0.06–1.4)	694 (273–5428)	697 (397–1990)
Final	36 (18–57)	0.57 (0.29–0.81)	–2.4 (5.7; 0.3)	0.3 (0.08–1.3)	295 (0.23–899)	426 (201–1120)
Age ≤2 years (n = 7)						
Baseline	13.7 (13–14.6)	0.15 (0.12–0.18)	–6.5 (–7; –6)	2 (0.21–3.1)	1005 (736–2839)	829 (290–1669)
Final	18.1 (17–18.8)	0.31 (0.29–0.33)	–4 (–4.2; –3.7)	0.45 (0.06–1.7)	422 (324–613)	493 (308–734)

Values are median (minimum–maximum). * BMD: Bone mineral density. ** NTX/Cr: urinary excretion of calcium and of *N*-telopeptide collagen cross-links/creatininuria.

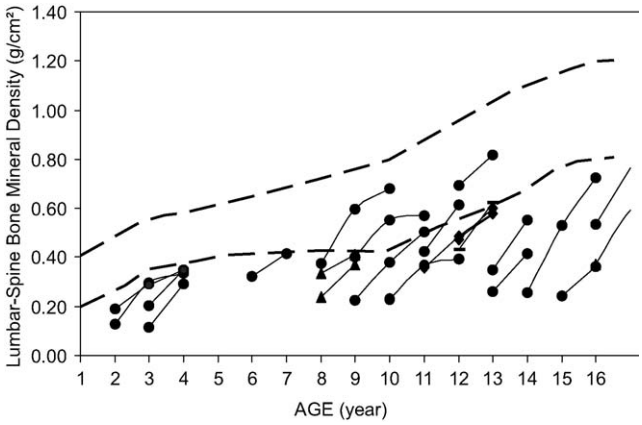

Fig. 1. Individual changes in bone mineral density of the lumbar spine in 24 children aged more than 1 year with osteogenesis imperfecta, receiving cyclic infusions of pamidronate. Normal values are from Glastre et al. [6].

Serum concentrations of calcium, phosphate, and PTH were normal in all children at baseline and at the end of the study. 25OH vitamin D was below the normal range in 10 patients at baseline. During the study, all patients received vitamin D supplementation, thus, there was an increase in 25OH vitamin D concentrations by the beginning of the treatment with a plateau thereafter (data not shown). During treatment, 15 children developed hypercalciuria, but renal ultrasound and KUB did not reveal nephrocalcinosis. Serum creatinine was normal in all children before the initiation of therapy and did not change with treatment.

Nineteen children developed a transient acute febrile reaction with flu-like syndrome during the first infusion cycle, which subsided on paracetamol. A recurrence of this reaction during the second or third infusion cycle was observed in five of them. A 2-month-old baby developed tremor due to hypocalcemia (1.9 mmol/l) during the first infusion, which resolved rapidly with IV administration of calcium and did not recur during subsequent cycles.

4. Discussion

This study confirms that pamidronate in cyclic infusions is an effective treatment in children with OI by decreasing two of the most debilitating factors of their disease: fractures and pain. No other medical treatments had been effective in OI, including those able to increase bone formation, such as fluoride or anabolic agents [18,19].

Because of the published results [9,10], we decided to conduct an open prospective study, judging unethical to conduct a placebo-controlled one. This may be a bias in the interpretation of the fracture incidence data, as it has been suggested a decrease in this incidence with age in OI [10]. Indeed, at baseline the fracture rate was higher in children less than 2 years than in others. However, we observed a decrease in fracture incidence in all age groups with treatment, although the PEDI showed that the mobility of children increased, which in turn increases the risk of fall and having fractures. Before treatment, fractures were either spontaneous or occurred after minor trauma, whereas fractures during therapy were the result of severe trauma or occurred in the presence of inappropriate rodding and/or severe bone deformity, two conditions making the occurrence of fracture unavoidable. At the spine we observed an increase in the vertebral area with reshaping of crushed vertebrae. Other studies have reported decrease in the fracture rate during treatment [9,12–14]. The magnitude of reduction in fracture rate was different between studies. This might be attributed to the different sample size, the degree of severity of the recruited cases, the different annual dose of pamidronate, and the calculation of the fracture rate before treatment. Previously, published studies compared the fracture incidence under treatment to the annualized fracture rate during the 1 or 2 years preceding the infusions whereas in our study, the fracture rate before treatment takes into account the whole life of the child. This might be a bias in the calculation of fracture rate because, as mentioned above, a decrease in the fracture rate has been described in children with OI. Moreover, waiting for the first fracture to determine the fracture rate further tends to increase the rate before treatment and therefore might have overestimated the results.

The increase in the mobility of children during treatment may be owing to the increase in muscle strength induced by treatment [20]. However, it is expected that the walking capacity, functional ability and autonomy increases as far as the children get older, therefore, in the absence of a control group, we cannot attribute the improvement in PEDI scores to the treatment.

We observed a dramatic decrease in pain during study. At the beginning of the treatment, pain was denied by some

patients who were not aware of it, as they got used to living with since birth. Actually, it was after receiving the first infusion that they realized what analgesia is. The decrease in the fracture incidence is of course a major cause of pain relief. However, it is unlikely that the marked reduction in pain that occurred a few weeks after the first infusion is related to reduction in clinical fracture rate. Changes in cytokines and reduced bone turnover are more likely factors. Some studies suggest that bisphosphonates may decrease bone pain in patients with osteolytic lesions, such as metastasis or multiple myeloma [21]. Due to the design of the study, we cannot speculate that pain reduction is related only to the effect of treatment, and further studies are needed on that point.

At baseline, half of the population had NTX/Cr ratio higher than normal, confirming the observation of Glorieux et al. [9] about the role of increase in bone resorption in OI. These high values may be related to unrecognised microfractures or clinical fractures with low mobility status. Nevertheless, although the evaluation was carried out before the infusions only, and that the nadir after each course was likely missed, we observed a dramatic decrease in these markers, in all children at the end of the study, indicating the pharmacological effect of the treatment. Similarly, to what has been reported in previous studies [12,14], the reduction in NTX/Cr exceeded the reduction in alkaline phosphatase (62% vs. 31%). BMD increased at the lumbar spine with improvement of the *Z*-scores and, when measured BMD at the femoral neck improved too. The lumbar spine BMD increment was higher than that observed by Giraud and Meunier [13] (55% vs. 27%) but very similar to the annual increase observed by others [9,12,14]. The decrease in fracture incidence, the increase in BMD along with the pattern of changes of biochemical markers reflect the positive effects of pamidronate on bone through decreasing bone resorption to a greater magnitude than bone formation.

The reason of efficacy of the treatment in the reduction of fracture incidence is speculative. In accordance with previous reports [9,12,14], we observed a large increase in BMD, as illustrated in Fig. 1. However, most of the patients had still a low BMD by the end of the study, although some of them reached the inferior limit of the normal range. Thus, although at a higher value, this BMD is still a risk factor for fractures. On the other hand, we observed a dramatic and rapid decrease in NTX, indicating a rapid effect of pamidronate on osteoclasts, i.e., a decreased osteoclastic activity, which is one of the determinants of bone fragility [9]. This effect may be associated with a preservation of some mechanical qualities of bone. Further studies are needed to assess the value of evaluation of biochemical markers in children treated with bisphosphonates.

We did not observe a delay in healing of fractures or osteotomy sites. However, the safety of long-term treatment with bisphosphonates on bone healing and stiffness of treated bone in children need careful studies and require validation with better measure of bone quality than DXA [22]. Skeletal deformities including kyphoscoliosis, long bone curvature, and epiphyseal destruction partially contribute to short stature in OI, which is related to the severity of the disease. In our study, the children were short for age since birth. During treatment, they grew-up following curves parallel to those of healthy children, thus despite an adequate growth, they remained below the average for age and no catch-up of growth was observed. Their weight also increased adequately with treatment but the children remained below the average for their age matched healthy children. However, the changes in weight were as expected for the changes in height, therefore the weight to height proportion was not affected by the treatment. One infant had severe refractory anorexia and did not grow up during the study with two SD decrease in his height and weight as compared to baseline.

In conclusion, our data confirm that, although non-curative, pamidronate is an effective symptomatic treatment, able to reduce fracture rate and pain in children with OI, including infants.

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